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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/519,998	03/06/2000	D. Scott Wilbur	33700W003	8767

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EXAMINER
WELLS, LAUREN Q

ART UNIT	PAPER NUMBER
1617	16

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/519,998	WILBUR ET AL.	
	Examiner	Art Unit	
	Lauren Q Wells	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-39 are pending. The Amendment filed 1/18/02, Paper No. 15, amended claims 1-2, 6-11, 14-15, 17-19, 21-23, 26-29, and added claims 31-39.

Response to Applicant's Arguments/Amendment

Applicant's arguments with respect to claims 1-30 have been considered but are moot in view of the new ground(s) of rejection. However, to the extent that the arguments may be relevant to the instant rejection, the Examiner will address them.

Applicant's amendment and arguments are sufficient to overcome the objections to the claims and specification in the previous Office Action.

Applicant's amendment and arguments are sufficient-in-part to overcome the 112 rejections in the previous Office Action. See below for details.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) The phrase "which is stabilized towards cleavage by biotinidase of the biotinamide bond to release biotin" in claim 1 (part b)) is vague and indefinite, as it is confusing. This phrase is unclear and is not understood.

(ii) The term "derivatives" in claim 32 is vague and indefinite, as is it not clear what compounds "EDTA derivatives" refer to. The specification does not further define this phrase

and one of skill in the art would not be apprised of its meaning, as the term "derivatives" encompasses an innumerable amount of chemical possibilities.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-25, 31-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilbur et al. (WO 97/29114).

Wilbur et al. teach biotin-containing compounds and biotinylation reagents incorporating soluble linker moieties. Biotin compounds disclosed include biotin, desthiobiotin, biotin sulfone, and iminobiotin. Homotrifunctional or heterotrifunctional linkers are disclosed, wherein these linkers may be coupled to a functional moiety and a biotin moiety and a third coupling site on the linker, wherein the third site may be radiolabeled and fluorescent molecules, proteins, peptides, antibiodies, and conjugating molecules. Linkers are disclosed as ranging from 6 to 50 atoms. Positron emitting radionuclides disclosed for use include F-18, Br-75, B4-76, and I-124. Water solubilizing biotin-chelate conjugates are disclosed, wherein EDTA, DTPA, NOTA, DOTA, and TETA are disclosed as chelates, and wherein the chelates may be attached to radionuclides. Streptavidin is disclosed as being cross-linked with biotin derivatives. Applications of these compounds include as targeting agents, diagnostic agents, or therapeutic agents. Disclosed (compound 56) is a trifunctional biotin-containing reagent comprising biotin, a conjugation

group (maleimide) and a radiohalogenated moiety. See Pg. 1, line 26-Pg. 7, line 2; Pg. 8, line 12-pg. 40, line 17.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26-30 rejected under 35 U.S.C. 103(a) as being unpatentable over Wilbur et al. as applied to claims 1-25 and 31-39 above, and further in view of Yau et al. (5,541,287) or Theodore et al. (5,578,287) and Maddock (5,474,772).

The instant invention is directed to a reagent comprising, a trifunctional cross-linking moiety and linkers, which link the moiety to an affinity ligand, an effector agent, and a bimolecular moiety, methods of using the reagent, and kits comprising the reagent.

Wilbur et al. fail to teach a method of diagnosing or treating and kits (see above disclosure).

Yau et al. teaches pretargeting methods and compounds. Certain embodiments of the compounds include chelate-biotin compounds and conjugates incorporating a chelate and a chemically modified biotin compound useful in diagnostic or therapeutic pretargeting methods. Disclosed is a method of diagnosis/treatment wherein an antibody-ligand conjugate is

administered followed by an anti-ligand compound that binds unbound antibody-ligand conjugate from the blood. Further disclosed is a kit. See Col. 1, line 42-Col. 2, line 50; Col. 4, line 49-Col. 7, line 3; Col. 95, line 22-line 35.

Theodore et al. teach three-step pretargeting methods using improved biotin-active agents. Preferred biotin-active agents include Y-90-DOTA-biotin conjugates. A method of diagnosis/treatment is disclosed wherein the antibody-ligand conjugate is administered followed by anti-ligand compound that clears unbound antibody-ligand conjugate from the blood. Further disclosed is a kit. See abstract; Col. 4, line 11-Col. 6, line 33; Col. 61, line 36-line 25.

Maddock teaches a method of therapeutic or diagnostic treatment comprising administering a medical agent and thereafter extracorporeally removing agent by passing bodily fluid over a support adapted to immobilize agent. See col. 1, line 15-Col. 2, line 1; Col. 4, line 65-Col. 6, line 2.Col. 9, line 29-Col. 10, line 46.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the teachings of Yau et al. or Theodore et al. into the invention of Wilbur et al. and obtain a method for diagnosis or treatment of a mammalian condition or disease and obtain a kit because a) Wilbur et al., Yau et al., and Theodore et al. all teach biotin conjugates as active agents for diagnostic and therapeutic use; b) Wilbur et al., Yau et al., and Theodore et al. all teach biotin as radiolabeled; c) Wilbur et al., Yau et al., and Theodore et al. all teach antibodies as targeting moieties; thus, since Wilbur teaches compounds similar to Yau and Theodore and since Wilbur teaches his compounds diagnostic and therapeutic purposes, one of skill in the art would have been motivated to teach the compounds of Wilbur in the diagnostic and therapeutic processes of Theodore or Yau et al.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of the combined references using the teachings of Maddock and obtain a method for diagnosis or treatment of a mammalian condition or disease comprising extracorporeally eliminating non-tissue-bound therapeutic or diagnostic biomolecule conjugates because a) Maddock teaches that his invention may be applied to nearly any treatment procedure with a medical agent that would benefit by artificial clearance, such as a cancer treating/diagnostic agent that is harmful when lingering in the body ; b) the combined references teach radiolabled biotin for use in treating cancer therapeutically and diagnostically.

112 Rejection Maintained

The rejection of claims 4-6, 14 and 30 under 35 U.S.C. 112 is MAINTAINED for the reasons set forth in the Office Action mailed 7/23/01, Paper No. 9, and those found below.

Regarding the phrases "derivatives, mutants, and fragments" and "essentially the same binding function", Applicant argues, "those of skill in the art would readily understand what is intended by these phrases and terms". This argument is not persuasive. The terms "derivatives", "mutants", and "fragments", encompass as innumerable amount of chemical possibilities and hence compounds. Since the specification does not define these terms and one of ordinary skill in the art could not be apprised of all the possible "derivatives", "mutants", and "fragments", this phrase is vague and indefinite. The term "essentially the same binding function" is vague and indefinite, as it is not clear what "essentially" refers to. The Examiner respectfully points out that compounds dissimilar to biotin could have "essentially the same binding function". Does Applicant intend to claim all these compounds? It is not clear what essentially means in reference to a binding function. Thus, the rejection of claims 4-6, 14, 30

102 Rejection Maintained

The rejection of claims 1-25 under 35 U.S.C. 102(b) as being unpatentable over Wilbur et al. (WO 97/29114) is MAINTAINED for the reasons set forth in the Office Action mailed 7/23/01, Paper No. 9, and those found below.

Applicant argues, "Wilbur, on page 13, also describes a trifunctional moiety which is linked to the biotin molecule via diaminopropane. However, contrary to the reagent of Applicants' invention, the trifunctional structure described in Wilbur is included to improve the solubility and not to bind to a biomolecule. None of the structures described by Wilbur contain the three essential moieties recited in Applicant's invention. . .The diaminopropane of Wilbur can not be regarded as a biomolecule and is not itself reactive with functional groups normally present on biological molecules. Furthermore, none of the structures described by Wilbur contain any protection against biotinidase and are therefore not particularly useful in vivo or in the presents of plasma in vitro". These arguments are not persuasive. First, the Examiner respectfully directs Applicant to page 39 of Wilbur, which discloses the exact same compound as that recited in claim 23 of the instant invention. Thus, the compound of page 39 of Wilbur does contain all three of the essential moieties recited in Applicant's invention. The arguments regarding diaminopropane are moot, as the structure on page 39 of Wilbur does not contain diaminopropane as the reactive moiety, but contains maleimide as the reactive moiety. Furthermore, it is respectfully pointed out that a compound and its properties are inseparable. In re Papesch. Thus, since Wilbur teaches the same compounds as that of the instant invention, the compounds of Wilbur must contain protection against biotinidase.

103 Rejection Maintained

The rejection of claims 1-26 and 28-30 under 35 U.S.C. 103(a) as being unpatentable over Wilbur et al. in view of Yau et al. (5,541,287) or Theodore et al. (5,578,287) and Maddock (5,474,772) is MAINTAINED for the reasons set forth in the Office Action mailed 7/23/01, Paper No. 9, and those found below.

Applicant argues, "While the biotin derivatives of Wilbur contain similar structures which play a part in the reagent of Applicant's claimed invention, Wilbur does not teach or fairly suggest any core guidelines of Applicants' invention". This argument is not persuasive, as it is not commensurate in scope with the instant claims. The Examiner respectfully points out that the instant claims are directed to a compound, a method of using that compound, and a kit comprising the compound. Thus, since Wilbur teaches the same compound as that of the instant invention, for the same use, Wilbur teaches the functional limitations of the instant claims and does not need to suggest any core guidelines of Applicants' invention, since a compound and its properties are inseparable.

Applicant argues, "Wilbur fails to teach or fairly suggest the presentation of a reagent capable of simultaneous binding of a defined ratio of affinity ligands and effectors to a biomolecule". This argument is not persuasive, as it is not commensurate in scope with the instant claims, which do not recite ratios of affinity ligands and effects to biomolecules.

Applicant argues, "Yau, Theodore, and Maddock all fail to teach or fairly suggest a reagent having three different moieties each serving a specific need of simultaneously labeling of targeting molecules for in vivo diagnostic and therapeutic applications in conjunctions with extracoporeal removal of non-targeted molecules from blood circulation. Yau, Theodore, and Maddock also fail to teach or fairly suggest a reagent having protection against biotinidase".

These arguments are not persuasive, as Yau, Theodore, and Maddock are relied upon merely for their teachings of kits and teaching that biotin compounds containing therapeutic or diagnostic agents are known for in vivo processes and uses.

Applicant argues, "there is nothing in Wilbur or Yau, Theodore, and Maddock which would motivate one of ordinary skill in the art to combine them as suggested in the Office Action". This argument is not persuasive, as all four of these references are directed to biotin conjugates as active agents for diagnostic and therapeutic use.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Q Wells whose telephone number is (703) 305-1878. The examiner can normally be reached on M-F (7-5:30), with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (703)305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

lqw
November 4, 2002

SREENI PADMANABHAN
PRIMARY EXAMINER 11/16/02